

The Man Behind the Molecules: John Maraganore's RNAi Legacy



The 2024 OTS lifetime achievement winner, John Maraganore, is best known for his pioneering role in making RNA interference (RNAi) a successful therapeutic modality while CEO at Alnylam Pharmaceuticals. However, before joining and after leaving Alnylam, he was and continues to be influential in the biotechnology sphere, with his leadership skills, optimism, and willingness to take risks still changing the RNAi landscape.

Biogen and Millennium Pharmaceuticals: drug developments and important acquisitions

Born in Chicago, Illinois, to Greek immigrant parents in 1962, Maraganore got his first microscope when he was six years old, and by high school, he was working at his dad's pathology lab. By 1986, Maraganore had earned his B.A., M.S., and PhD in Biochemistry and Molecular Biology and began his career as a post-doctoral research scientist at Upjohn in Kalamazoo, Michigan.

In 1987, Maraganore joined Biogen, where he played a [crucial role](#) in developing a blood thinner drug called bivalirudin, which was commercially known as Angiomax. It was during a Biogen meeting that Nobel Prize winner Walter Gilbert gave a presentation, after which Maraganore became convinced that genomics would make a big difference in medicine.

"People were skeptical about being able to make money on genomics, but, frankly, I was a bit frustrated that Biogen was not more active in this area," [Maraganore said](#).

In 1997, after a decade at Biogen, he joined Millennium Pharmaceuticals, where he held various leadership roles, including general manager of their Biotherapeutics subsidiary and vice-

president of mergers, acquisitions, and strategic planning. At Millennium, he led their [protein drug development work](#) and made a [deal to acquire](#) LeukoSite, the biotech that discovered the successful blood cancer drug Velcade. While enjoying his work at Millennium, Maraganore was unaware that another presentation would soon bring about a massive life change.

RNA interference: a stunning discovery

In early 2001, Maraganore received a call from [Phillip Sharp](#) asking if Millennium Pharmaceuticals was interested in learning more about his research on RNAi and mammalian cells. At the time, Maraganore admits he didn't know much about RNAi or its potential relevance in human therapies, but he knew Sharp from his Biogen days and invited him and his collaborators to give a presentation.

During the meeting, Maraganore said he and his Millennium colleagues were stunned by the science. At Millennium, they were currently in the throes of functional genomics, using complex techniques to determine the function of specific genes.

"When we saw the ability of silencing an mRNA with these small interfering RNA molecules, it was a stunning observation," [he said](#).

Within days of the meeting, Maraganore called Sharp to tell him Millennium was interested in an exclusive license to the RNAi IP for research and was open to investing in a new company to explore the therapeutic potential of siRNA. However, Sharp and his team were hesitant about starting a therapeutics company at the time. Instead, they countered with a nonexclusive license, making Millennium one of the first to license [Tuschl I and Tuschl II](#) patents for research use.

It was in early 2002 that Maraganore began to hear about the beginnings of a new company focusing on RNAi therapeutics and that summer, he was asked to be CEO of Alnylam. Despite being happy at Millennium, Maraganore found himself thinking about this new company as he drove to work in the morning, dreaming up all the potential things they could do with the science. He had caught the RNAi bug and, despite his Millennium colleague's warnings and skepticism that it would take too long for the science to become something tangible, Maraganore couldn't say no to the opportunity.

"For me [it] was just the [uniqueness of this potential platform](#) that we could build and the therapeutic applications that I thought could be really disruptive, and that's what got me to go."

Alnylam: pioneering RNAi therapeutics

Today, Alnylam is the leader in RNAi medicines, but when Maraganore started in 2002, it was just a small, venture-backed [startup](#) with the idea of making drugs in a completely different way.

"John has always been able to see the power of science and how it can be translated to medicines," [said Akshay Vaishnav](#), Chief Innovation Officer at Alnylam.

"John's vision was both simple and bold, which was to really translate this beautiful, endogenous mechanism for RNAi into an entirely new class of medicines," said [Martin Maier](#), SVP of research at Alnylam.

However, the company's ultimate success wasn't without its challenges or outward cynics, with a key hurdle being how to deliver the RNAi drugs to the target tissues.

"How do you get these molecules inside the cell? They need to act, and, you know, not surprisingly, that took longer than people hoped it would," Maraganore said.

From 2005 to 2009, Maraganore said the company formed numerous pharmaceutical alliances, the enthusiasm for the technology's potential spurring companies to invest. However, these alliances grew disillusioned with how long the technology was taking, and [Maraganore said](#) they were also trying to fit RNAi into their specific therapeutic areas of interest.

"As opposed to saying, let's just go where the technology takes us and make medicines where the technology takes us, [the companies were] proverbially putting the round peg into the square hole."

Regrettably, in 2010, the pharmaceutical industry began to lose interest in RNAi, and a significant investment blow came in September 2010 when Novartis, which had bought into Alnylam early on, decided not to expand its \$100 million option for nonexclusive rights to [Alnylam's technology](#). Soon after this, Roche also dropped their investment, and it was apparent that the early 2000s RNAi boom had become a bust.

Maraganore said the outside world "[literally thought we were dead](#)," and contacts and friends in the industry would ask if he was okay, suspecting that Alnylam was done. Meanwhile, Alnylam was looking at their scientific data and, despite the external difficulties and reduced stock value, felt they had finally made progress on solving delivery. Still, it was a tough time for the company, and Alnylam had to let [25% of its workforce go](#); at the start of 2012, another 33% followed suit. Maraganore said this was one of the most painful decisions as CEO and was determined to find new roles for the departing employees, reviewing a list of affected individuals and their potential new job prospects at a board meeting every week.

This challenging time was handled masterfully by Maraganore, his former Alnylam colleagues [stated](#), noting that he was still able to keep employees believing in the potential of RNAi despite their financial losses and outward critics.

The RNAi express: listening to the science

"You may remember the story of a little kid with the jingle bell, and he alone can hear the bell ringing," [Maraganore said](#). The story of the Polar Express and the little boy who believed in something that couldn't be seen is how Maraganore felt about RNAi. He and the rest of the people at Alnylam could hear the bells, and they needed the doubters to listen to them, too.

To make the bells ring louder, they needed more human clinical data.

"So during that period of remarkable adversity, where everybody thought we were gone, and everybody thought we were never going to make it, we had those inklings of data that gave us encouragement," [he explained](#).

In 2011, the company created '[Alnylam 5 x 15](#)', a strategy to advance RNAi therapeutic programs focusing on the liver into clinic development by 2015. By the end of 2015, Alnylam had surpassed its goal and had eight programs in clinical development. With the success of Alnylam 5 x 15, it was time to set a new five-year goal: bring three or more RNAi therapeutics to market by the end of 2020.

"The beauty of the five-year plans, which served to reduce strategic doubt and second-guessing, was the way our employees adopted them as a rallying cry," [Maraganore said](#). "It gave our team harmonization and an understanding of why these goals were important to the company and our ultimate mission of bringing medicines to patients."

Even with the 5 X 15 goal, Maraganore made sure his employees were exploring their own scientific interests as well, encouraging them to spend 20% of their time pursuing their ideas, which led to some of Alnylam's great breakthroughs, including how to [deliver](#) GalNAc to the liver.

It took Alnylam 16 years to turn their research into a successful business, but it is now one of the largest biotechnology companies in the world, and under Maraganore's leadership, it brought to market the first four RNAi therapeutic medicines: Onpattro (patisiran), Givlaari (givosiran), Oxlumo (lumasiran), and [Legvio \(inclisiran\)](#). These drugs target specific genetic disorders by [silencing the genes](#) responsible for the diseases, offering new treatment options for patients with previously unmet medical needs. The bells of RNAi were now ringing clearly for all.

After Alnylam: mentorship and industry leadership

Over the summer of 2021, as the COVID-19 pandemic continued, Maraganore reflected on life and the next steps he wanted to take. His leadership had placed Alnylam on a bright path to continue to grow, innovate, and deliver new medicines, but he now felt like he was operating on autopilot.

"I also became excited about where the industry was going...with the science out there," [he said](#). "And ultimately talked to my board, stating...that late August and into the fall, that maybe this is the right time for me to transition."

[Maier](#) said that Maraganore's unwavering optimism, perseverance, and his willingness to take risks were instrumental in the success of Alnylam. Now, Maraganore is using these skills to help future Alnylam's grow and thrive. After stepping down from Alnylam, he founded JMM Innovation, LLC, where he focuses on advancing transformative medicines through investment and advisory services. He's accomplishing this via [three "buckets"](#).

First, he's working with venture groups like Arch Venture Partners, Atlas Ventures, Blackstone Life Sciences, and RTW Investments, allowing him to mentor emerging biotech companies and guide strategic investments in innovative therapies.

"I'm working with those groups on the investment side to basically help make sure that new companies that get started have a solid foundation and can obviously generate disruptive new medicines for the future," [he said](#).

The second bucket is getting involved on a few boards. Currently, he's on the boards of biotechnology companies Beam Therapeutics, Kymera Therapeutics, Rapport Therapeutics, and Takeda Pharmaceuticals. Additionally, he is involved with privately held companies like Aera Therapeutics, Aitia Bio, Hemab Therapeutics, and Orbital Therapeutics.

"And then the final bucket, which is really where I'm spending a lot of time, is to mentor new CEOs and then advise them in building their companies," [he explained](#). "And that's a non-fiduciary type role where I really want to help that next generation of leaders think about how to build their business and how to be successful at the end of the day."

Maraganore says he loves mentoring young, emerging entrepreneurs, especially from diverse backgrounds, and focuses on people trying to build exciting scientific endeavors. "I do think there's something important about giving back and helping grow a little bit more of a diverse repertoire of future leaders for the industry, and so I am passionate about that."

"He's been an incredible resource and mentor for me, and I'm one person, and there are hundreds of people who can say that," [said Rachel Meyers](#), former head of research and RNAi development at Alnylam.

His biggest advice to those trying to build a company or innovate is to follow the science and to be bold and courageous even when the outside world may doubt you.

City Therapeutics: innovation in the RNAi field

His latest venture brings him back to the sphere of RNA interference medicines. Maraganore co-founded City Therapeutics with venture capitalists, scientists, and other Alnylam veterans and will serve as the executive chair.

"At Alnylam, we launched the birth of RNAi therapeutics as a new class of medicines," Maraganore said in a [statement announcing City's debut](#). "We see the potential for RNAi to emerge as the next major category of high-impact medicines, rivaling if not exceeding the success of monoclonal antibodies."

"New innovation is needed to realize this future, and we believe City Therapeutics can lead this next chapter," he added.

Maraganore is also on the advisory board of Judo Bio, another biotech startup aiming to improve RNAi medicine. Additionally, he co-chairs, with Dr. Stanley Crooke, the advisory council

for the [n-Lorem Foundation](#), a nonprofit organization that strives to provide experimental antisense oligonucleotide (ASO) based treatments to patients with [ultrarare diseases](#), and is also the chair of Hemab Therapeutics' board of directors, contributing to the development of innovative therapies for rare bleeding disorders.

John Maraganore's journey from a post-doctoral research scientist to the CEO of Alnylam Pharmaceuticals underscores the transformative power of innovative thinking and tenacity. His early experiences at Biogen and Millennium Pharmaceuticals equipped him with the vision to embrace the potential of RNA interference (RNAi) as a revolutionary therapeutic platform, and despite facing skepticism and significant challenges, Maraganore's ability to hear the RNAi bells enabled Alnylam to become a leader in the field. His story illustrates not only the importance of perseverance in the face of adversity but also underscores how visionary leadership can drive the evolution of medical science, ultimately improving patient outcomes and reshaping the landscape of therapeutic development.